Evaluation of a Population With Occupational Exposure to Airborne Ammonium Perchlorate for Possible Acute or Chronic Effects on Thyroid Function

John P. Gibbs, MD
Riaz Ahmad, MD, MPH
Kenny S. Crump, PhD
David P. Houck, MS
Terisita S. Leveille, RN, MS
Joyce E. Findley, RN, BSN
Michael Francis

Evaluation of a Population With Occupational Exposure to Airborne Ammonium Perchlorate for Possible Acute or Chronic Effects on Thyroid Function

John P. Gibbs, MD
Riaz Ahmad, MD, MPH
Kenny S. Crump, PhD
David P. Houck, MS
Terisita S. Leveille, RN, MS
Joyce E. Findley, RN, BSN
Michael Francis

Employees at an ammonium perchlorate production facility in Nevada and a larger control population from the same chemical complex without direct AP exposure were monitored extensively for airborne perchlorate exposure. Single-shift and working-lifetime cumulative dose estimates were made using standard breathing-rate estimates and assuming rapid absorption, based upon solubility. Calculated single-shift doses ranged from 0.2 to 436 μg/kg, with an average of 36 μg/kg. Working-lifetime cumulative doses in the higher exposure group ranged from 8,000 to 88,000 μg/kg, with an average of 38,000 μg/kg. Thyroid profiles, including free thyroxine index and thyroid-stimulating hormone level, were obtained both before shift and after shift to assess thyroid-axis perturbation due to single working-shift perchlorate exposure. Thyroid-function data were also analyzed with respect to estimates of cumulative exposure to assess any measurable chronic effects on thyroid gland function. Additionally, standard clinical blood test parameters of liver, kidney, and bone marrow function were evaluated to assess any measurable chronic effects of perchlorate exposure on those organs. Multiple regression was used to assess the effects of exposure variables and demographic variables on organ function parameters. No perchlorate-attributable effects on thyroid, bone marrow, kidney, or liver function were detected.

From the Health Management Division, Kerr-McGee Corporation, Oklahoma City, Okla. (Dr Gibbs, Mr Houck, Ms Findley), and Kerr-McGee Chemical Corporation, Henderson, Nev. (Ms Leveille, Mr Francis); the University of Oklahoma Health Sciences Center, Oklahoma City, Okla. (Dr Ahmad); and ICF Kaiser, Ruston, La. (Dr Crump).

Address correspondence to: John P. Gibbs, MD, Health Management Division, Kerr-McGee Corporation. PO Box 25861, Oklahoma City, OK 73125.

1076-2752/98/4012-1072$3.00/0

Ammonium perchlorate (AP) has been used as an oxidizer component in solid propellants for rockets, missiles, and fireworks for over 50 years. AP is highly soluble in water, where it dissociates into its component ions and can persist for many decades under typical ground- and surface-water conditions. Most of the United States' AP production over the past half century has been at two separate facilities near Las Vegas, Nevada, because of the high electricity and low humidity requirements for the process and storage of AP.

Recent (April 1997) advances in the analytical detection capability for low concentrations of perchlorate have resulted in the lowering of the reporting threshold from 400 to 4 parts per billion (ppb). As a result, perchlorate has been discovered in groundwater near various manufacturing sites in California, Nevada, and Utah. Perchlorate has also been detected at ppb levels in Lake Mead and in the Colorado River downstream from Lake Mead, which together serve as a drinking-water source for approximately 20 million people in Nevada, Arizona, and southern California.

Our knowledge of the health effects of perchlorate in humans derives primarily from studies and reports on patients with Graves' disease. Potassium perchlorate was widely used in the treatment of hyperthyroidism during the 1950s and early 1960s. The perchlorate ion

readily absorbs systemically from the gastrointestinal tract. Its physiological effect is to reversibly inhibit iodide uptake in the thyroid, thereby lowering thyroid hormone levels and controlling the symptoms of hyperthyroidism. Alterations in thyroid function are thought to be the most sensitive potential effect from low-level environmental contamination. Perchlorate is excreted unchanged by the kidneys with a half-life of approximately 6 hours.[1]

Studies of perchlorate in Graves' disease patients range in duration from a single dose[2] to several weeks.[3–11] One case study[12] reports treatment with perchlorate in a single patient for 22 years. Doses of perchlorate range from < 1 mg/kg per day[13] to > 20 mg/kg per day,[4] with typical doses in the range of 6–14 mg/kg per day. The effects observed include the blockage of iodide uptake and iodide discharge by thyroid,[2] gastrointestinal irritation, skin rash,[3,4] and hematological effects, including agranulocytosis and lymphadenopathy.[4,6] Seven cases of fatal aplastic anemia were reported during the period 1961–1966 at doses of 6–14 mg/kg per day.[5,7–11]

Two studies examined the effects of perchlorate in healthy volunteers. Burgi et al[13] studied perchlorate at a dosage of 9.7 mg/kg per day on five subjects for 8 days, and Brabant et al[14] studied perchlorate at a dosage of 12 mg/kg per day on five subjects for 4 weeks. Both studies observed effects on the thyroid at these doses.

Perchlorate is currently used in several European countries to prevent hyperthyroid side effects from an antiarrhythmic cardiovascular drug, amioderone. Patients are typically treated with doses up to 14 mg/kg per day, and usage in this context has not been reported to result in aplastic anemia.

Perchlorate is still available in the United States for administration (200–400 mg given by mouth) ½ to 1 hour prior to the administration of $NaTcO_4$ for brain, blood pool imaging, and placenta localization. Perchlorate ions block the uptake of $^{99}TcO_4^-$ ions in the choroid plexus, salivary, and thyroid glands.

Employees at the two AP facilities in the United States have historically been exposed to perchlorate occupationally through the respiratory and possibly through the oral routes. Significant absorption of perchlorate through intact skin is unlikely; however, significant systemic absorption of inhaled perchlorate through mucous membranes in the respiratory and gastrointestinal tracts is likely because of its high aqueous solubility at body temperature.

No specific Occupational Safety and Health Administration standard for perchlorate exists, and it has been categorized as a nuisance dust, with an 8-hour time-weighted average permissible exposure limit of 15 mg/m^3. Safety concerns because of its explosion potential have been considered to outweigh any risk of pharmacologic effect from exposure. In 1988, one of the two facilities near Las Vegas blew up and was subsequently rebuilt in Utah. Commercial production of AP was discontinued in June 1998 at the facility near Las Vegas, which left the Utah plant as the only production facility in the United States.

This study was started in September 1997 to determine the levels of perchlorate exposure, both acute and chronic, among workers at the AP production facility near Las Vegas and to determine if there are any measurable adverse effects on thyroid, bone marrow, kidney, or liver function, using routine clinical blood tests. New exposure and biological monitoring data were obtained and analyzed in conjunction with previously obtained medical surveillance data at the facility.

Methods

Study Timeline

This study was carried out at an AP production facility and an associated AP crossblending facility near Las Vegas. A medical surveillance program was started at those facilities in 1994, which included a blood test (complete blood count and serum chemistry tests), a medical history, and an examination by a physician. For 12 months, starting in early January 1996, a thyroid panel was added to the blood test. In early 1997, evaluation of the 170 thyroid tests obtained in 1996 did not indicate any difference between perchlorate-exposed employees and those without exposure; however, no exposure estimates were available.

In September 1997, a campaign was initiated to obtain pre-shift and post-shift thyroid profiles on as many employees as possible, both exposed and non-exposed (all voluntary) and to fully characterize exposures. In all, 133 employees volunteered for pre-shift and post-shift blood tests, and 24 full-shift breathing-zone exposure measurements (with detectable levels of AP) were made. In March 1998, another campaign was initiated to measure worker exposures, using a much more sensitive analytic method. This time, 95 full-shift personal breathing zone exposure measurements and 25 full-shift area exposure measurements were made. In addition, 16 more pre-shift and post-shift blood tests were obtained on the more highly exposed employees during this same time period. In October 1997, the sale of the AP business was announced, and commercial production of AP at the facility ceased in June 1998.

Exposure Assessment

Personal breathing zone sampling methods. Full-shift sampling was carried out under the direction of a certified industrial hygienist using 5-μm polyvinyl chloride filters in 37-mm closed-face cassettes. Air was sampled at a rate of 2.0 liters per minute, using standard industrial hygiene sampling pumps that were calibrated daily.

Analytical methods. The September 1997 laboratory analysis of the filter cassettes, based on quantifica-

tion of the ammonium ion using National Institute for Occupational Safety and Health method 6016 (LabCorp Analytics, Richmond, VA), had a minimum reporting limit of approximately 17 $\mu g/M^3$. The March 1998 analysis carried out at the Montgomery Watson Laboratory in Pasadena, California, using 300.0 modified EPA methodology (ClO_4^- determination using ion chromatography), had a minimum reporting limit of approximately 0.04 $\mu g/M^3$. With this method, perchlorate was detectable in all plant areas and in many offices of employees who frequented the AP process areas, whereas with the September 1997 analysis a large percentage of the samples were reported as nondetectable. Exposure levels in the dustier areas of the facility appeared to compare quite well.

Exposure Groups

Eight homogeneous exposure groups were defined, based upon similar job activities and exposure potential. These included a control group, whose members were never in the production areas; maintenance workers and foremen, who were casually in the production areas; and six discrete operator job categories. Multiple samples were taken for each of these groups (total of 119 personal breathing zone samples) to determine the distribution of exposures for that group. For the control employees working in other, non-AP areas of the plant, exposures were estimated using the 19 full-shift area samples that were collected in areas of the plant where the majority of the control employees worked.

Employees in one of the dustiest homogeneous exposure groups routinely wore respirators during the dustier job cycles. When a respirator was used intermittently during the dustier activities, the exposure concentration was adjusted downward by 65%, based upon two full-day assessments when the industrial hygienist changed filter cassettes every time the employee put a respirator on or took it off.

Dose Estimation

Dose was estimated by:

$$[\textit{respiratory rate}] \times [\textit{inhalation concentration}] \times [\textit{exposure duration}] \times [\textit{fraction absorbed}]$$

Respiratory rates of 0.0068 M^3/kg per hour and 0.0165 M^3/kg per hour were estimated for sedentary and active workers, respectively, based on work by Beals et al.[15] Active workers in this study were assumed to perform work in the "moderate" category from Beals et al, which included walking 2–3 miles per hour, woodworking, yard work, house work, and car repair, while sedentary workers were presumed to perform work characterized by the "low" activity group. Average weights of 89 kg and 74 kg, respectively, for men and women were used, based upon company medical records. Daily respiration volumes for an active 70-kg worker are thus 9.2 M^3 over an 8-hour shift and 13.9 M^3 over a 12-hour shift.

The estimated fraction absorbed is based on work by Boecker[16] with CsCl in beagles. That study indicated that, on average, 78% of inspired CsCl aerosol (based on breathing rates and average air concentrations) was retained initially in the animals. Because of its high aqueous solubility at body temperature, it was assumed that AP is similarly absorbed.

Single-shift dose estimates. The exposure duration was taken as the time elapsed between the pre-shift and post-shift blood tests. The exposure concentration was directly measured for that shift.

Working-lifetime dose estimates. Personnel records were reviewed and employees were interviewed to determine the number of years worked in each of the seven homogeneous exposure groups. An average of 2,000 hours worked yearly was assumed, based upon typical overtime rates at the facilities. Each subject's working-lifetime cumulative dose was then estimated as:

$$\Sigma[\textit{mean group exposure}] \times [\textit{years in exposure group}] \times 2{,}000$$

Biological End Points

Thyroid function. The standard clinical thyroid profiles included a total serum thyroxine assay (T_4), triiodothyronine resin uptake assay (T_3U), and an ultra-sensitive thyroid-stimulating hormone (TSH) assay. The free T_4 index (FTI), calculated as the product of the T_4 and T_3U assays, is considered the best estimate of free T_4. Two different clinical reference laboratories were used in this study. LabCorp (Kansas City, MO) was used for the 1996 thyroid profiles at the time of routine medical surveillance exams. Associated Pathologists Labs (Las Vegas) was used during 1997–1998 for thyroid blood tests collected before and after shifts. This selection was made primarily because of the laboratory's close proximity to the production facility.

Bone marrow function. Standard assays from the complete blood count obtained during medical surveillance examinations in 1996, 1997, and 1998 were used to assess hematopoietic function. These included the hemoglobin level (HGB), hematocrit value (HCT), red blood cell count (RBC), mean corpuscular volume (MCV), white blood cell count (WBC), and platelet count. All tests were performed by LabCorp in Kansas City.

Kidney and liver function. Standard serum chemistry values obtained during medical surveillance examinations in 1996, 1997, and 1998 were used to assess kidney and liver function. Tests of kidney function included serum creatinine level and blood urea nitrogen (BUN) level. Tests of liver function included serum glutamyl pyruvic transaminase (SGPT), serum glutamyl oxaloacetic

transaminase (SGOT), γ-glutamyl transpeptidase (GGTP), and alkaline phosphatase. All tests were performed by LabCorp in Kansas City.

Study Designs

The single-shift thyroid effects study was designed to detect any measurable transient effects on the thyroid axis due to exposure on a single day. Participation in this study was voluntary on the part of the employees. Employees taking thyroid medications were intentionally not discouraged from volunteering for blood tests in order to protect their medical confidentiality and to encourage honest self-reporting of thyroid medication status. Nominal rewards were offered to encourage participation. All employee exposure days (24 exposure days for 18 different individual employees) were identified during which breathing zone exposure monitoring was conducted on the same day that the individual volunteered for pre-shift and post-shift blood thyroid tests.

All employees who volunteered for blood tests in 1997 and 1998 completed a one-page questionnaire indicating whether or not they had had worked in the AP process area in the preceding 30 days, how much they had slept in their last sleep period, and when they had awoke. The time of day that each blood sample was taken was recorded. For each employee in the exposed groups, a shift dose estimate was made based upon exposure monitoring for that specific shift and the elapsed time between the pre-shift and post-shift blood tests. For this study, the control group (92 employees) was selected from all employees who volunteered for pre-shift and post-shift thyroid function tests and who indicated that they had not worked in an AP area in the preceding 30 days. Nine employees who indicated that they were taking or had ever been advised to take thyroid medication were excluded from either group for statistical analysis (all controls, reducing the control group to 83). Thirty employees with a history of exposure within the preceding 30 days but who were not monitored during the specific shift that the blood tests were taken were also excluded from statistical analysis (but were included in the working-lifetime study).

Working-lifetime thyroid effects study. Of the 254 employees at the plant, 170 employees had a thyroid function test with their medical surveillance examination in 1996. In addition, 130 employees (294 blood tests) volunteered for pre-shift and post-shift thyroid studies in 1997 and 1998. Employees who had never worked in any jobs with AP exposure, based upon personnel records, were identified as the control group, and dose estimates were made, based upon area monitoring for perchlorate and job type (sedentary or active). Cumulative dose estimates were made for the remainder of the employees for whom thyroid function data existed. The exposed group arbitrarily stratified into a high-cumulative-dose group (>8,000 μg/kg) and a low-cumulative-dose group (<8,000 μg/kg). As with the single-effects study, any employees indicating that they were taking or had been advised to take thyroid medication were excluded (nine controls, two from the high-dose group). Medical records were reviewed and employees questioned if either the TSH or FTI was more than 3 standard deviations from the mean, to assure the lack of a known clinical diagnosis.

Working-lifetime kidney, liver, and bone marrow function study. Using the group defined for the working-lifetime thyroid effects study, all routine blood tests from medical surveillance examinations in 1996, 1997, and 1998 were identified. Standard tests on the blood panel were selected as indicative bone marrow, kidney, or liver functions. Working-lifetime perchlorate doses were estimated for the date that each blood sample was collected.

Statistical Methods

Multiple regression was used to study the relationships between measures of thyroid function, bone marrow function, liver function, or kidney function, and various potential explanatory variables. A sequential approach was used to determine whether a dependent variable would be log-transformed and whether any outliers would be eliminated from an analysis. First, an ordinary multiple regression was applied to all of the data, using the untransformed dependent variable. If the residuals from this regression were significantly non-normal ($P < 0.05$) by the Wilk-Shapiro test,[17] the regression was repeated using the log-transform of the dependent variable. If these residuals were found to be significantly non-normal, the regression using the untransformed variable was repeated, with outliers omitted. (An outlier was defined statistically as a value whose corresponding residual was larger in absolute value than three standard deviations.) Finally, if these residuals were found to be non-normal, the regression was repeated using the log-transformed independent variable and with outliers eliminated. (However, log-transforms were not considered in analyses of the single-shift study.) The multiple regression reported herein was from the data set for which residuals were found to be satisfactorily normally distributed ($P > 0.05$).

Once a data set with normally distributed residuals was obtained, a regression was performed that took account of the fact that multiple measurements were made on the same subject. This regression was conducted using the MIXED procedure in SAS,[17] and permitted multiple measurements on the same individual to be correlated.

The dependent variables evaluated in the single-shift study were the cross-shift change (post-shift minus pre-shift) in measures of thyroid function, T_3U, T_4, FTI, and TSH.

TABLE 1
Exposure Characterization of Homogeneous Exposure Groups (all exposures in μg perchlorate/m³)

Group	*n*	AVG	STD	MIN	P_{25}	MED	P_{75}	MAX
Controls	19	0.036	0.052	0.000	0.000	0.018	0.036	0.194
Maintenance and Foremen	25	23.6	28.1	1.2	5.2	9.6	31.3	104.3
Operations job 1	10	20.6	27.1	2.4	4.4	6.8	26.8	94.0
Operations job 2	11	369.0	776.5	6.4	29.3	40.5	208.3	2,740.7
Operations job 3	14	92.4	54.0	18.2	52.0	73.1	130.5	183.9
Operations job 4	13	267.4	284.6	29.6	63.3	169.3	336.8	971.6
Operations job 5†	32	614.6	813.1	20.6	81.6	313.3	625.8	3,350.0
Operations job 6	14	627.0	759.0	62.7	178.1	383.8	655.5	3,070.0

* AVG, average; STD, standard deviation; MIN, minimum; P_{25}, 25th percentile; MED, median; P_{75}, 75th percentile; MAX, maximum.
† Respirators routinely worn on job 5 for the dustier operations.

The non-perchlorate explanatory variables used in the acute study were race, gender, age, hours awake prior to pre-shift test, number of hours slept during the most recent period of sleep prior to testing, time of day (indicator of whether or not pre-shift test was conducted between 6 AM and 6 PM) and shift length (8 or 12 hours). The perchlorate variable used was the single-shift exposure estimate in μg/kg per day.

The dependent variables evaluated in the working lifetime study were measures of thyroid function (T_3, T_4, FTI, TSH), measures of hematological function (HGB, HCT, RBC, MCV, WBC, platelets), measures of liver function (SGOT, SGPT, GGTP, alkaline phosphatase) and measures of kidney function (BUN, creatinine). The non-perchlorate explanatory variables used in the working-lifetime study were age, gender, and race. For thyroid tests, an additional explanatory variable was added to indicate whether the measurement was from a routine physical examination in 1996, a pre-shift examination in 1997–1998, or a post-shift examination in 1997–1998. The perchlorate dose variables used were group (control, low-dose, or high-dose) and estimated total working lifetime cumulative perchlorate dose in μg/kg. The group variable and estimated total working lifetime perchlorate dose were not both used in the same analysis; rather, the analyses described above were conducted twice, once using a group variable and once using the estimated total dose variable.

Contingency table analyses[17] were performed to evaluate whether the percentage of individuals with elevated TSH, low FTI, low HGB, low WBC or low platelet count (defined as out of the normal ranges for these end points provided by the laboratories) was different among controls, low-dose, and high-dose groups. These analyses were performed both using individual test results as the basic sampling unit (ignoring the fact that multiple tests were performed on the same individual) and using individuals as the basic sampling unit, by assigning an individual the common result of multiple tests when all tests on the individual were in agreement and eliminating individuals (no more than five in any analysis) whose test results were not in agreement.

Results

Exposure Characterization for Homogeneous Exposure Groups

A summary of the exposure characterization for the eight homogeneous exposure groups is presented in Table 1. Although the controls' exposure was detectable, it was several orders of magnitude lower than those of the exposed groups. Maintenance and first-line supervisors who were casually in the area were grouped together and had a significantly lower exposure than all but one of the operations jobs. The measured exposures in this table do not account for occasional respirator use.

Single-Shift Study

Results from the single-shift study are presented in Tables 2, 3, and 4 and in Figs. 1 and 2. Residuals were normally distributed ($P \geq 0.05$) in each case. As shown in Table 2, exposures were monitored on a total of 18 different workers (24 separate shifts) on shifts that the worker volunteered for pre-shift and post-shift blood tests. Estimated doses ranged from 0.2–436 μg/kg per day, with a mean and median of 36 and 13 μg/kg per day, respectively. Table 3 demonstrates that exposure (dose estimate) was not a significant predictor of the cross-shift change in any of the thyroid parameters (P values ranged from 0.52 to 0.94). The only significant finding was that cross-shift TSH changes were greater for those who worked 12-hour shifts than for those who worked 8-hour shifts.

Of the exposed group, 25% worked 8-hour shifts and 75% worked 12-hour shifts, while 76% of the controls worked 8-hour shifts and 24% worked 12-hour shifts. The cross-shift TSH difference correlated strongly with shift duration ($P = 0.01$), with the 12-hour shift accounting in a 0.45 UIU/mL increase across the shift. Table 4 details the cross-shift difference in TSH by group and by shift duration. No other statistically significant correlations were detected in cross-shift changes in the

TABLE 2
Thyroid Function Test Results From the Single-Shift Study*

Group	Dose Est	Age	Tenure	Time†	Pre-Shift T_3U	Pre-Shift T_4	Pre-Shift FTI	Pre-Shift TSH	Post-Shift T_3U	Post-Shift T_4	Post-Shift FTI	Post-Shift TSH
Controls‡												
AVG	—	44.9	12.5	8.6	29.3	7.5	2.1	2.2	29.0	7.5	2.1	2.2
STD	—	9.2	8.5	1.5	3.5	1.8	0.4	1.2	4.4	1.8	0.4	1.1
SEM	—	1.0	0.9	0.2	0.4	0.2	0.0	0.1	0.5	0.2	0.0	0.1
P_{25}	—	38.1	5.7	7.8	27.4	6.4	1.9	1.5	26.8	6.6	1.9	1.4
MED	—	44.4	10.9	8.2	29.1	7.3	2.2	2.1	28.8	7.3	2.2	2.0
P_{75}	—	51.1	17.7	8.9	31.8	8.3	2.4	2.8	30.9	8.2	2.4	2.7
Exposed§												
AVG	36.2	41.2	9.3	10.2	29.8	7.0	2.1	2.2	29.4	7.3	2.1	2.5
STD	85.2	10.1	7.2	2.4	2.0	1.4	0.5	1.2	2.2	1.2	0.4	1.5
SEM	17.4	2.1	1.5	0.5	0.4	0.3	0.1	0.3	0.5	0.2	0.1	0.3
P_{25}	6.7	32.9	3.9	9.1	28.4	6.0	1.8	1.5	28.5	6.2	1.8	1.7
MED	13.3	37.2	6.7	11.3	29.3	7.0	2.1	2.0	29.1	7.5	2.2	2.1
P_{75}	35.7	49.1	12.3	11.8	30.7	8.2	2.4	2.5	31.4	8.2	2.4	3.3

* Dose Est, dose estimate; T_3U, triiodothyronine resin uptake; T_4, total serum thyroxine; FTI, free T_4 index; TSH, thyroid stimulating hormone; SEM, standard error of the mean.
† Hours between pre-shift and post-shift blood tests (>9 hours = 12-hour shift).
‡ Control group characteristics: 83 tests; 83 individuals; 65 males, 18 females; 63 8-hour shifts; and 20 12-hour shifts.
§ Exposed group characteristics: 24 tests; 18 individuals; 15 males, 3 females; 6 8-hour shifts; 18 12-hour shifts.

TABLE 3
Multiple Regression *P* Values From the Single-Shift Study

Parameter	Cross-Shift Change T_3U	T_4	FTI	TSH
Dose Estimate	0.83	0.88	0.94	0.52
Age	0.84	0.80	0.80	0.75
Gender	0.30	0.38	0.95	0.46
Race	0.25	0.83	0.43	0.06
Hours sleep*	0.45	0.32	0.43	0.85
Hours awake*	0.49	0.44	0.44	0.36
Shift time†	0.20	0.31	0.59	0.18
Shift duration‡	0.36	0.51	0.46	**0.01**

* Hours sleep, reported hours slept during last sleep period; Hours awake, hours awake before starting shift.
† Shift time was stratified into 6 AM–6 PM or 6 PM–6 AM at the start of shift.
‡ Shift duration = 8 hours or 12 hours.
Boldface indicates $P \leq 0.05$.

TABLE 4
Analysis of Cross-Shift TSH Change

Group	12-Hour Shifts	8-Hour Shifts
Controls		
Number	20	63
Average	+.25	−.13
Exposed		
Number	18	6
Average	+.38	+.12

thyroid parameters and explanatory variables tested.

Working-Lifetime Study

Results from the working-lifetime study are presented in Tables 5 through 7 and in Figs. 3 and 4. Residuals were reasonably normally distributed ($P \geq 0.04$), except for SGPT ($P = 0.0008$). As shown in Tables 5 and 6, working-lifetime perchlorate dose estimates ranged from 500 to 7,000 (mean = 3,500) μg/kg for the low-dose group and from 8,000 to 88,000 (mean = 38,000) μg/kg for the high-dose group. Tenure for the two exposure groups combined ranged from 1 to 27 years (mean = 8.3).

As shown in Table 7, no significant correlations with estimated lifetime cumulative perchlorate dose were detected in any of the measures of thyroid, bone marrow, liver, or kidney function. Using the stratified groups in the regression analyses, the white blood cell count was higher for the low-dose group than for the control or high-dose groups ($P = 0.04$). No other significant group effects were detected. Thyroid tests appeared to differ statistically between the two reference laboratories used, but no age or gender associations were noted for TSH or FTI.

Statistically significant gender and race differences were apparent in the clinical tests of bone marrow function, liver function, and kidney function. Hemoglobin, hematocrit, SGPT, GGTP, and creatinine values were all slightly lower in females relative to males. Black workers had slightly lower hemoglobin and hematocrit values and slightly higher creatinine levels relative to white workers.

A separate analysis was performed to evaluate the number of blood tests and individuals with elevated values for TSH, low FTI, low HGB, low WBC or low platelet count in each group. No exposure-attributable effect of perchlorate was apparent when we looked for these specific abnormalities.

Discussion

The data presented in this report clearly show that at the inhalation exposure levels typical at the Henderson AP facility, there was no observable trend toward thyroid,

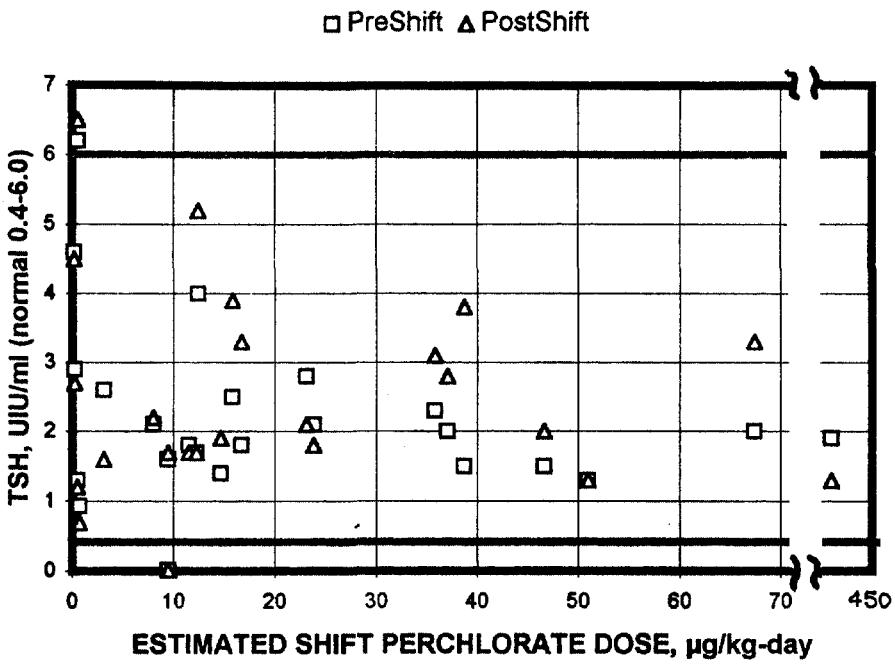

Fig. 1. Thyroid-stimulating hormone (TSH) levels in the single-shift study.

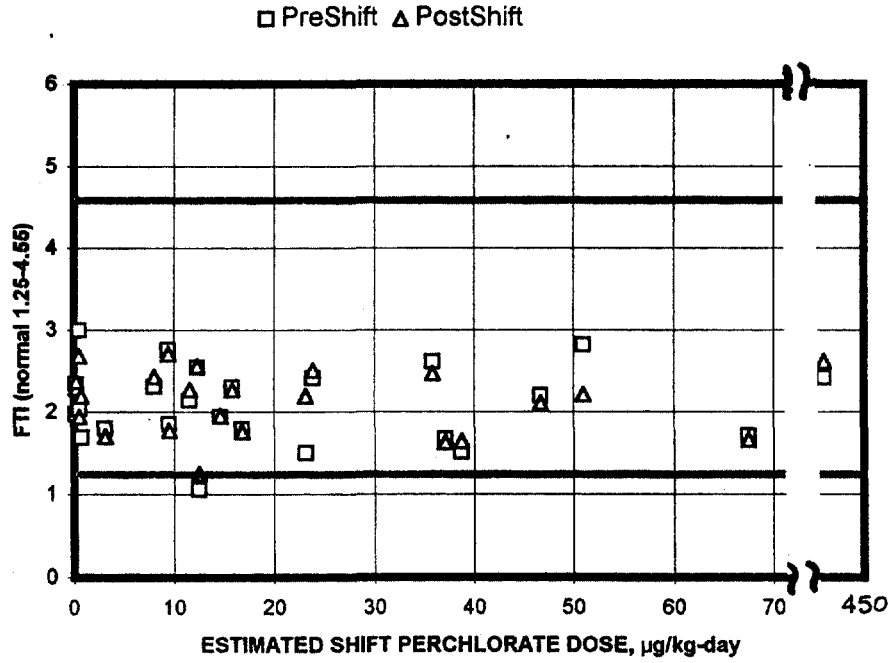

Fig. 2. Free thyroxine (T_4) index (FTI) in the single-shift study.

bone marrow, kidney, or liver toxicity as measured with routine clinical blood tests. The correlation of shift duration with cross-shift change in TSH is consistent with published reports of circadian changes in serum TSH levels.[18–20] The majority of employees started their shifts within 1 to 4 hours of awakening. The end of an 8-hour shift would coincide with the end of the plateau in TSH levels prior to the evening rise in levels. The end of a 12-hour shift would coincide with a period when TSH has started to rise or has been rising for a few hours.

Average single-shift exposures in this study were 36 µg/kg per day, while the maximum single-shift exposure was 436 µg/kg per day, equivalent to 0.4% and 4%, respectively, of the daily dose that was typical in the treatment of Graves' disease (6,000–14,000 µg/kg per day). Average working-lifetime cumulative doses for the high- and low-dose groups were 38,000 µg/kg and 3,500 µg/kg, respectively, over an average 8.3-year period of time. These average working-lifetime cumulative doses are equivalent to one-half and five times the daily dose typically given as treatment for Graves' disease for the low- and high-dose groups, respectively. The highest cumulative perchlorate dose in this study (88,000 µg/kg over 10 years) is equivalent to the cumulative dose typically prescribed in the treatment of Graves' disease over approximately 2 weeks.

The concern being addressed in this study, however, is that of low-level exposure through drinking water, not exposures through the respiratory route. At this time, there are no reports in the literature specifically on the absorption of perchlorate salts through the respiratory route in humans or in animals. Principles of chemistry and physiology, along with limited data on AP and other soluble salts, strongly support the assumption made in this report that the majority of inhaled perchlorate was absorbed.

The exposure of concern is the perchlorate ion and not the particular perchlorate salt. Perchlorate salts dissociate completely when dissolved in water or aqueous tissues. The solubility of AP in water at body temperature is approximately the same as that of sodium chloride. One would expect that inhaled AP would rapidly dissolve on moist mucous membranes in the nose, throat, mouth, or lungs, except for a small fraction that could be inhaled and exhaled without contacting a moist mucous membrane.

TABLE 5
Thyroid Function Test Results From the Working-Lifetime Study

Group	Dose	Age	Tenure	T_3U	T_4	FTI	TSH
1996 Examinations—LabCorp*							
Controls							
AVG	75	43.7	10.6	32.0	8.14	2.54	2.25
STD	59	10.0	7.8	3.4	1.43	0.44	1.76
SEM	5	0.9	0.7	0.3	0.13	0.04	0.16
P_{25}	23	36.9	4.1	30.0	7.20	2.20	1.40
MED	64	42.8	9.2	32.0	8.10	2.60	1.82
P_{75}	114	51.6	16.3	34.0	9.10	2.80	2.59
Low-dose							
AVG	3,369	44.3	5.8	32.1	8.26	2.58	1.81
STD	1,771	8.1	3.7	2.7	1.41	0.41	0.71
SEM	347	1.6	0.7	0.5	0.28	0.08	0.14
P_{25}	2,037	39.3	2.8	30.0	7.30	2.25	1.40
MED	3,323	43.3	5.6	32.0	8.15	2.55	1.92
P_{75}	4,048	49.0	7.6	34.0	9.28	2.88	2.16
High-dose							
AVG	28,629	39.9	8.8	31.9	8.07	2.35	2.34
STD	21,038	7.2	5.7	4.8	2.09	0.68	2.51
SEM	4,485	1.5	1.2	1.0	0.44	0.14	0.53
P_{25}	10,732	34.3	4.3	31.0	6.73	2.13	1.32
MED	20,723	39.7	7.7	32.0	7.75	2.35	1.64
P_{75}	41,562	46.3	11.9	34.0	8.88	2.78	2.27
1997–1998 Study—Associated Pathologists Laboratories†							
Controls							
AVG	93	45.7	14.0	29.3	7.54	2.17	2.25
STD	65	9.9	9.1	3.5	1.64	0.35	1.28
SEM	5	0.8	0.7	0.3	0.13	0.03	0.10
P_{25}	38	38.3	6.8	27.2	6.60	1.95	1.40
MED	96	44.4	14.4	28.9	7.40	2.20	1.90
P_{75}	131	53.6	18.9	31.8	8.28	2.43	2.70
Low-dose							
AVG	3,649	46.9	7.3	28.3	7.87	2.22	2.54
STD	1,661	6.5	3.6	2.0	1.47	0.41	0.93
SEM	41	2.6	1.9	1.4	1.21	0.64	0.96
P_{25}	2,470	41.8	4.9	27.4	6.65	1.94	1.90
MED	3,409	45.5	7.1	28.3	8.20	2.28	2.50
P_{75}	4,504	50.9	9.3	29.2	8.85	2.47	3.10
High-dose							
AVG	40,773	40.1	9.5	30.1	7.23	2.15	2.26
STD	23,263	8.2	6.0	4.0	1.60	0.47	1.70
SEM	2,509	0.9	0.6	0.4	0.17	0.05	0.18
P_{25}	23,405	34.9	4.6	28.5	6.13	1.81	1.33
MED	37,256	37.5	8.6	29.5	6.85	2.15	1.85
P_{75}	59,612	48.3	12.4	31.6	8.28	2.41	2.60

* 1996 Examinations LabCorp group characteristics—Controls: 120 tests; 120 individuals; 101 males, 19 females. Low-Dose: 26 tests; 26 individuals; 20 males, 6 females. High-Dose: 22 tests; 22 individuals; 19 males, 3 females.

† 1997–1998 Study Associated Pathologists Laboratories group Characteristics—Controls: 150 tests; 72 individuals; 60 males, 12 females. Low-Dose: 40 tests; 18 individuals; 13 males, 5 females. High-Dose: 86 tests; 31 individuals; 27 males, 4 females.

In humans, approximately 50% of particulates 10 microns in diameter are deposited in the mouth and throat, and 50% are deposited in the bronchial, bronchiolar, or alveolar region of the lung.[21] Particulates less than 10 microns in diameter are deposited relatively more in the lung regions, while particulates greater than 10 microns in diameter are deposited relatively more in the mouth and throat. Particulates that are deposited in the mouth and throat, as well as many of those depositing in the trachea and bronchi, will be presented to the gastrointestinal tract for absorption (thus directly comparable to AP in drinking water). Since the perchlorate ion is excreted unchanged in the urine, it is unlikely that there is any first-pass effect on absorbed perchlorate in the liver, gut, or lung.

Studies[22–25] in beagles in the 1960s using $^{137}CsCl$, a highly soluble radioactive salt, supports the assumption that AP is rapidly absorbed

TABLE 6
Liver, Kidney, and Hematological Test Results From the Working-Lifetime Study*

				Liver				Kidney		Bone Marrow					
Group	Age	Tenure	Dose	SGOT	GGTP	SGPT	ALKP	BUN	CREAT	WBC	RBC	HGB	HCT	MCV	PLT
Controls†															
AVG	44.3	11.4	76	24.4	42.7	25.8	79.6	15.0	1.03	6.56	4.872	15.03	45.34	93.1	236.7
STD	9.57	7.9	56	13.9	102.2	12.9	26.7	3.9	0.17	1.98	0.346	1.21	3.53	4.7	49.6
SEM	0.6	0.5	5	0.9	6.4	0.8	1.7	0.2	0.01	0.12	0.022	0.08	0.22	0.3	3.1
P_{25}	38.1	4.6	25	18.0	18.0	17.0	61.0	12.0	0.90	5.23	4.650	14.30	43.20	90.0	203.3
MED	43.8	10.7	67	22.0	29.0	23.0	74.0	15.0	1.00	6.20	4.890	15.10	45.20	93.0	232.0
P_{75}	51.5	16.7	114	27.8	42.8	30.0	94.8	18.0	1.10	7.40	5.100	15.80	47.80	96.0	262.0
Low-dose‡															
AVG	45.4	6.6	3,329	24.4	33.6	27.1	83.5	14.6	1.01	7.36	4.980	15.24	46.05	92.6	223.1
STD	7.05	3.5	1,796	10.2	21.4	18.2	27.9	3.4	0.17	2.39	0.334	1.26	3.32	4.2	56.4
SEM	0.94	0.5	312	1.4	2.9	2.4	3.7	0.5	0.02	0.32	0.045	0.17	0.44	0.6	7.5
P_{25}	40.5	3.7	2,048	18.0	17.8	16.0	65.0	12.0	0.90	5.58	4.803	14.30	43.85	90.0	175.5
MED	44.3	6.6	3,001	21.5	28.0	21.5	77.0	14.5	1.00	6.60	5.040	15.25	45.95	93.0	229.0
P_{75}	50.3	8.1	4,309	27.0	41.0	33.3	93.8	17.0	1.10	8.30	5.213	16.03	48.30	95.0	265.8
High-dose§															
AVG	40.1	9.7	29,561	29.9	71.6	77.4	86.6	15.7	1.04	6.54	4.965	15.01	45.21	91.2	229.9
STD	7.62	5.8	21,417	36.7	207.4	332.5	58.5	4.5	0.20	1.91	0.356	0.90	2.75	3.9	52.2
SEM	1.11	0.8	4,057	5.4	30.2	48.5	8.5	0.7	0.03	0.28	0.052	0.13	0.40	0.6	7.6
P_{25}	34.4	5.2	10,521	18.0	18.0	16.5	62.5	12.5	1.00	5.10	4.730	14.55	43.45	89.0	193.0
MED	39.8	7.9	21,940	22.0	28.0	22.0	79.0	14.0	1.10	6.20	4.920	15.00	45.30	92.0	225.0
P_{75}	46.9	13.6	47,501	28.5	41.5	34.0	94.0	19.5	1.10	7.70	5.115	15.55	47.15	94.0	269.0

* SGOT, serum glutamyl oxaloacetic transaminase; GGTP, γ-glutamyl transpeptidase; SGPT, serum glutamyl pyruvic transaminase; ALKP, alkaline phosphatase; BUN, blood urea nitrogen; Creat, creatinine; WBC, white blood cell count; RBC, red blood cell count; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; PLT, platelet count.
† Control group characteristics: 258 tests; 133 individuals; 112 males, 21 females.
‡ Low-dose group characteristics: 56 tests; 27 individuals; 21 males, 6 females.
§ High-dose group characteristics: 47 tests; 25 individuals; 22 males, 3 females.

TABLE 7
Multiple Regression *P* Values* From the Working-Lifetime Study*

	Thyroid		Bone Marrow				Liver		Kidney	
Parameter	FTI	TSH	HGB	HCT	WBC	PLT	SGPT	GGTP	Creat	BUN
Group	0.34	0.92	0.18	0.14	**0.04**	0.17	0.82	0.81	0.77	0.33
Dose est	0.19	0.72	0.49	0.46	0.26	0.93	**N/A**	0.33	0.85	0.77
Age	0.12	0.72	0.40	**0.05**	0.45	**0.05**	0.35	**0.05**	0.85	0.45
Gender	0.23	0.76	**0.0001**	**0.0001**	0.90	0.06	**0.0001**	**0.0001**	**0.0001**	0.07
Race	0.28	**0.04**	**0.02**	0.10	0.27	0.27	**0.01**	0.39	**0.001**	0.73
Ref lab	**0.0001**	0.10	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**

* Ref lab, laboratory reference value. N/A, not applicable. Boldface indicates $P \leq 0.05$.
† *P* values for Age, Gender, Race, and Ref lab are the arithmetic average of *P* values obtained using Group and Dose est.

systemically through respiratory exposure. Calculations using estimates of the air volumes inspired and measured ^{137}Cs air concentrations indicated that an average of 78% (69%–87%) of the total inspired ^{137}Cs was deposited initially in these animals. The metabolism and dosimetry of ^{137}Cs was shown to be similar for the inhalation and intravenous routes of dosing. There was rapid translocation of inhaled ^{137}Cs to other tissues so that ^{137}Cs concentration in the lung became one of the lowest among the tissues analyzed. Because the ^{137}Cs was rather uniformly distributed throughout the body, the whole body was considered the critical organ for dosimetry purposes.

Thyroid disorders are relatively common in the general population[25–30] and increase with age, with females typically having a higher prevalence than males. Because of the difference in the age groups of study populations and differences in definitions of hypothyroidism and hyperthyroidism, it is difficult to compare the prevalence of these diseases in our study with those in other US studies. Comparison with one study (Remedios et al[28]), however, is possible. The study's authors se-

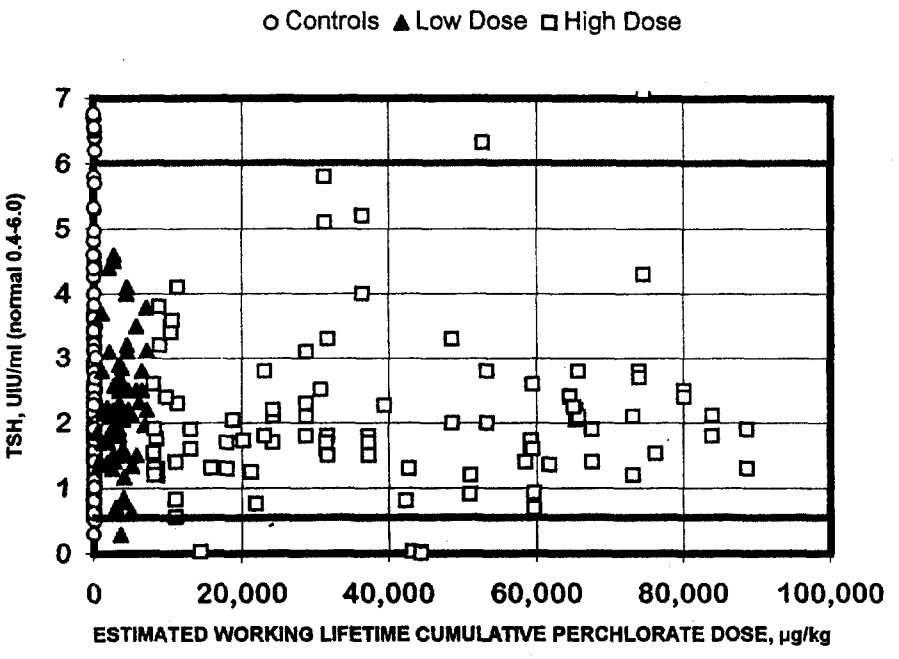

Fig. 3. TSH levels in the working-lifetime study.

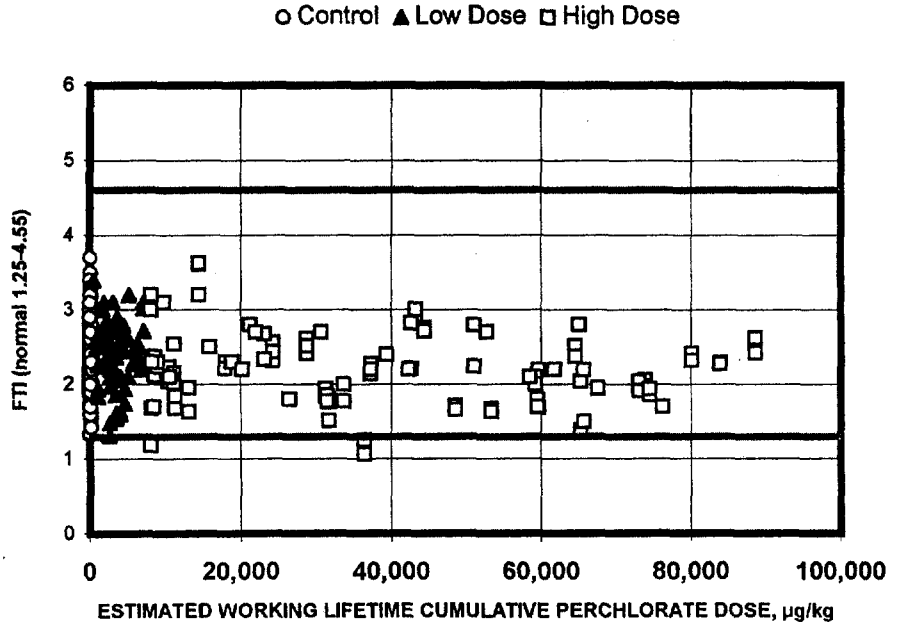

Fig. 4. FTI in the working-lifetime study.

lected a group of 2,606 adults from northern California who had no known history of thyroid disease and stratified the group by FTI. Eighty-seven percent of their population had an FTI between 1.41 and 3.40, while in our study none of the FTIs in the controls or exposed subjects were below 1.06 or above 3.70, and 96.4% of our population's FTIs were between 1.41 and 3.40. Age and gender were not found to correlate significantly with indices of thyroid function; however, the number of females in our study was relatively low (17%) and the age range relatively narrow (mean = 43.8, standard deviation = 9.4).

Conclusions

Calculated perchlorate doses from occupational exposures to airborne AP dust during the manufacture and crossblending of AP are two to three orders of magnitude less than doses historically prescribed in the treatment of Graves' disease. These same doses are two to three orders of magnitude greater than that which would result from consumption of water from Lake Mead or the Colorado River. Calculated working-lifetime cumulative dose over an average of 8.3 years is up to ten times the cumulative dose that would result from drinking water from Lake Mead or the Colorado River for a lifetime. No exposure-related effects on thyroid gland function (either acute or chronic) and no chronic exposure–related effects on bone marrow, liver, or kidney function were found.

Acknowledgments

The authors would like to thank Dr Joan Dollarhide, Dr Michael Dourson, and Dr Steven Lamm for their encouragement and advice on this study and Dr Roger McClellan for his assistance in finding references documenting the absorption and distribution of airborne soluble salts. We wish to thank the Employee Relations Department at the Kerr-McGee Henderson facility for scheduling tests and for their work in reviewing personnel records for work history. Lastly, we would like to thank the employees of Kerr-McGee Chemical LLC in Henderson and Apex, Nevada, for their cooperation, without which this study would not have been possible.

References

1. Eichler O. On the pharmacology of perchlorate. *Arch Exp Pathol Pharmacol.* 1929;144:251–260.
2. Stanbury J. Wyngaarden effect of perchlorate on the human thyroid gland. *Metabolism.* 1952;1:533–539.
3. Godley A, Stanbury J. Preliminary experience in the treatment of hyperthyroidism with potassium perchlorate. *J Clin Endocrinol.* 1954;14:70–78.
4. Crooks J, Wayne E. A comparison of potassium perchlorate, methylthiouracil, and carbimazole in the treatment of thyrotoxicosis. *Lancet.* 1960;1:401–404.

5. Krevans J, Asper S, Rienhoff W. Fatal aplastic anemia following use of potassium perchlorate in thyrotoxicoses. *JAMA.* 1962;181:162–164.
6. Morgans M, Trotter W. Potassium perchlorate in thyrotoxicosis. *Br Med J.* 1960;2:1086–1087.
7. Hobson Q. Aplastic anaemia due to treatment with potassium perchlorate. *Br Med J.* 1961;1:1368–1369.
8. Johnson R, Moore W. Fatal aplastic aneamia after treatment of thyrotoxicosis with potassium perchlorate. *Br Med J.* 1961;1:1369–1371.
9. Fawcett J, Clark C. Aplastic anemia due to potassium perchlorate. *Br Med J.* 1961;1:1537.
10. Gjemdal N. Fatal aplastic anaemia following use of potassium perchlorate in thyrotoxicosis. *Acta Med Scand.* 1963; 174:129–131.
11. Barzilai D, Sheinfeld M. Fatal complications following use of potassium perchlorate in thyrotoxicosis. *Israel J Med.* 1966;2:453–456.
12. Connell J. Long-term use of potassium perchlorate. *Postgrad Med J.* 1981;57: 516–517.
13. Burgi H, Benguerel M, Knopp J, Kohler H, Studer H. Influence of perchlorate on the secretion of non-thyroxine iodine by the normal human thyroid gland. *Eur J Clin Invest.* 1974;4:65–69.
14. Brabant G, Bergmann P, Kirsch C, Kohrle J, Hesch R, Muhlen A. Early adaptation of thyrotropin and thyroglobulin secretion to experimentally decreased iodine supply in man. *Metabolism.* 1992; 41:1093–1096.
15. Beals J, Funk L, Fountain R, Sedman R. Quantifying the distribution of inhalation exposure in human populations: Distribution of minute volume in adults and children. *Environ Health Prospect.* 1996; 104:974–979.
16. Boecker B. Comparison of cesium metabolism in the beagle dog following inhalation and intravenous injection. *Health Phys.* 1969;16:785–788.
17. SAS Institute Inc. *SAS/STAT® User's Guide, Version 6,* 4th ed, vols 1 and 2. Cary, NC: SAS Institute, Inc.; 1989.
18. Adriaanse R, Brabant G, Prank K, Endert E, Wiersinga W. Circadian changes in pulsatile TSH release in primary hypothyroidism. *Clin Endocrinol.* 1992;37: 504–510.
19. Kanabrocki E, Graham L, Veatch R, et al. Circadian variations in eleven radioimmunoassay variables in the serum of clinically healthy men. *Prog Clin Biol Res.* 1987;227A:317–327.
20. Weibel L, Brandenberger G, Goichot B, Spiegel K, Ehrhart J, Follenius M. The circadian thyrotropin rhythm is delayed in regular night workers. *Neurosci Lett.* 1995;187:83–84.
21. Camner P, Anderson M, Philipson K, et al. Human bronchiolar deposition and retention of 6, 8, and 10 micron particles. *Exp Lung Res.* 1997;23:517–535.
22. Boecker B, McClellan R. The effects of solubility on the bioassay for inhaled radionuclides. In: Kornberg, H, Norwood W, eds. *Diagnosis and Treatment of Deposited Radionuclides. Symposium XVIII.* Amsterdam, The Netherlands: Excerpta Medica Foundation; 1968:34–242.
23. Boecker B, Redman H, Chiffelle T, et al. Toxicity of inhaled $^{137}CsCl$ in beagle dog. *Fission Prod Inhal Proj.* 1969;Nov: 36–45.
24. McClellan R, Rosenblatt L, Bielfelt S, Boecker B. Eearly mortality from inhaled $^{90}SrCl$, $^{91}YCl_3$ and $^{144}CeCl_3$ and intravenously injected $^{137}CeCl$ in Beagle dogs. *Fission Prod Inhal Proj.* 1969;Nov:59–60.
25. Baldwin D, Rowett D. Incidence of thyroid disorders in Connecticut. *JAMA.* 1978;239:742–744.
26. Nolan J, Nancy J, Dibenedetto G. Case finding for unsuspected thyroid disease: costs and health benefits. *Am J Clin Pathol.* 1985;83:346–355.
27. Rallison M, Dobyns B, Meikle A, Bishop M, Lyon J, Stevens W. Natural history of thyroid disorders: prevalence, incidence, and regression of thyroid disease in adolescence and young adults. *Am J Med.* 1991;91:363–370.
28. Remedios L, Weber P, Feldman R, Schurr D, Tsoi T. Detecting unsuspected thyroid dysfunction by free thyroxin index. *Arch Intern Med.* 1980;140:1045–1049.
29. Sawin C, Geller A, Kaplan M, Bacharach P, Wilson P, Hershman J. Low serum TSH in older persons without hyperthyroidism. *Arch Intern Med* 1991;151:165–68.
30. Sawin C, Castelli W, Hershman J, McNarma P, Bacharach P. The aging thyroid: thyroid deficiency in the Framingham study. *Arch Intern Med.* 1985;145: 1386–1388.